

What is claimed is:

1. A method for discrimination of p16<sup>INK4a</sup> overexpressing metaplasias from p16<sup>INK4a</sup> overexpressing neoplastic or preneoplastic lesions in biological samples in the course of cytological testing procedures comprising
  - 5           a. determining the presence or absence of cells overexpression of p16<sup>INK4a</sup> in said biological sample;
  - b. determining the presence or absence of cells expressing at least one high risk HPV gene-product in said biological sample;
  - c. assessing simultaneous presence of cells expressing high risk HPV gene-products  
10           with cells overexpressing p16<sup>INK4a</sup> or the presence of cells overexpressing p16<sup>INK4a</sup> alone;
  - d. wherein the simultaneous presence of cells expressing high risk HPV gene-products with cells overexpressing p16<sup>INK4a</sup> is indicative for neoplastic or preneoplastic lesion.
2. A method according to claim 1, wherein the high risk HPV gene-products are predominately  
15           expressed in early neoplastic and/or preneoplastic lesions.
3. A method according to any one of the preceding claims, wherein at least one of the HPV gene-products is encoded by the HPV E7 gene.
4. A method according to claim 1, wherein at least one of the HPV gene-products is encoded by HPV E2 and/or E6 genes.
- 20   5. A method according to claim 1, wherein at least one of the HPV gene-products is encoded by HPV L1 and/or L2 genes.
6. A method according to any one of the preceding claims, wherein the HPV gene-product is a polypeptide or an RNA molecule.
7. The method according to any one of the preceding claims, wherein the neoplastic or  
25           preneoplastic lesions are lesions of the anogenital tract.
8. The method according to claim 7, wherein the lesion of the anogenital tract is a lesion of the uterine cervix.
9. A method according to any preceding claim, wherein the biological sample is a sample containing cells of anogenital origin.

10. A method according to claim 9, wherein the cells are cells originating from the uterine cervix.
11. A method according to claim 10, wherein the biological sample is a Pap-smear or a cytological preparation of the cervix uteri.
12. A method according to any one of the preceding claims, wherein the detection of the HPV gene-products and of the p16<sup>INK4a</sup> molecules is performed using at least one probe specifically for the molecules to be detected.
13. A method according to claim 12, wherein the probe is detectably labelled.
14. A method according to claim 13, wherein the label is selected from the group consisting of a radioisotope, a bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, or an enzyme.
15. A method according to any one of the claims 12 to 14, wherein the probe is a protein and/or a nucleic acid.
16. A method according to claim 15, wherein at least one probe is an antibody directed against a high risk HPV encoded geneproduct or p16<sup>INK4a</sup>.
17. The method according to claim 16, which comprises an immuno-cytochemical staining procedure.
18. The method according to claim 15, wherein at least one probe is a nucleic specifically hybridizing to a high risk HPV geneproduct.
19. The method according to claim 18, which comprises an in situ hybridization reaction.
20. The method according to claim 18, which comprises a nucleic acid amplification reaction.
21. The method according to claim 20, wherein the nucleic acid amplification reaction is PCR or LCR.
22. A method according to any of the preceding claims, wherein detection reactions using nucleic acid probes and polypeptide probes are carried out simultaneously.
23. A method according to any one of the preceding claims, wherein the high risk HPV gene-products are gene-products of the cancer associated HPV subtypes HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56 and 58.
24. A method according to any of the preceding claims, wherein overexpression of p16<sup>INK4a</sup> simultaneous to expression of at least one high risk HPV geneproduct in at least one single cell is determined.

25. A kit for performing the method according to any one of the preceding claims, which is a diagnostic kit or a research kit, comprising

- a. probes for the detection of the presence or absence of the overexpression of p16<sup>INK4a</sup> in biological samples
- 5      b. one or more probes for the detection of the presence or absence of the expression of one or more HPV gene-products in biological samples.

26. A kit according to claim 25 furthermore comprising

- a. a p16<sup>INK4a</sup> sample for carrying out a positive control reaction
- b. one or more samples of HPV gene-products for carrying out positive control reactions.